abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Specification:

Please cancel the existing Sequence Listing (pages 1-31) for the captioned application, replace it with the substitute Sequence Listing (pages 1-28) appended hereto, and insert the same at the end of the application.

Please substitute pending paragraph [0018] with the following paragraph [0018]:

Briefly stated, the present invention provides isolated nucleic acid molecules encoding a PS1 gene product. A representative nucleic acid molecule is provided in Fig. 2A-Fig. 2F (SEQ ID NO:3), while in other embodiments, nucleic acid molecules are provided which encode a mutant PS1 gene product that increases the probability of Alzheimer's disease (in a statistically significant manner). One representative illustration of such a mutant is an amino acid substitution at residue 263, wherein, for example, an arginine may be substituted for a cysteine (C263R) (SEQ ID NO:28). Another representative illustration of such a mutant is an amino acid substitution at residue 264, wherein, for example, a leucine may be substituted for a proline (P264L) (SEQ ID NO:30). A third representative illustration of such a mutant is an amino acid substitution

at residue 269, wherein, for example, a histidine may be substituted for an arginine (R269H) (SEQ ID NO:32).

Please substitute pending paragraph [0019] with the following paragraph [0019]:

Other aspects of the present invention included isolated nucleic acid molecules, selected from the group consisting of: a) an isolated nucleic acid molecule as set forth in Fig. 2A-Fig. 2F (SEQ ID NO:3), or complementary sequence thereof; b) an isolated nucleic acid molecule that specifically hybridizes to the nucleic acid molecule of (a) under conditions of high stringency; and c) an isolated nucleic acid that encodes a PS1 gene product. As utilized herein, it should be understood that a nucleic acid molecule hybridizes "specifically" to a PS1 gene (or related sequence) if it hybridizes detectably to such a sequence, but does not usually hybridize to the PS2 gene sequence under the same conditions. The invention also provides methods of obtaining said nucleic acid molecules, fragments thereof, or functional derivatives thereof.

Please substitute pending paragraph [0021] with the following paragraph [0021]:

The present invention further provides isolated proteins comprising a PS1 gene product, as well as PS1 peptides of greater than 12, 13, or 20 amino acids. Within one embodiment, a protein is provided that has the amino acid sequence set forth in Fig. 2A-Fig. 2F (SEQ ID NO:4). Within another embodiment, the protein is a mutant PS1 gene product that increases the probability of Alzheimer's disease. Such mutants include

those with an amino acid substitution at residue 263 (*e.g.*, an arginine:cysteine substitution), or at residue 264 (*e.g.*, a leucine:proline substitution), or at residue 269 (*e.g.*, a histidine:arginine substitution). In addition, PS1 peptides are provided which are composed of 13 to 20 amino acids derived or selected from the N-terminal, internal, or carboxyl-terminal hydrophilic regions.

Please substitute pending paragraph [0025] with the following paragraph [0025]:

The present invention further provides nucleic acid probes which are capable of specifically hybridizing (as defined below) to a PS1 gene under conditions of high stringency. Within one related aspect, such probes comprise at least a portion of the nucleotide sequence shown in Fig. 1A-Fig. 1F or Fig. 2A-Fig. 2F (SEQ ID NO:1 or 3), or its complementary sequence, the probe being capable of specifically hybridizing to a mutant PS1 gene under conditions of high stringency. Within one particularly preferred aspect, probes are provided that are capable of specifically hybridizing to a mutant PS1 gene encoding a protein in which amino acid residue 263 is changed from cysteine to arginine, or in which amino acid 264 is changed from proline to leucine, or in which amino acid 269 is changed from arginine to histidine, each under conditions of very high stringency. Representative probes of the present invention are generally at least 12 nucleotide bases in length, although they may be longer. Also provided are primer pairs capable of specifically amplifying all, or a portion of, any of the nucleic acid molecules disclosed herein.

Please substitute pending paragraph [0035] with the following paragraph [0035]:

Fig. 1A-Fig. 1F depicts the nucleotide sequence of the normal S182 gene, PS1 locus (SEQ ID NO:1). Within the coding region, beneath each line of nucleotide sequence are the corresponding putative amino acid residues (amino acid position in Fig. 1A-Fig. 1F: 83-549 (SEQ ID NO:2), 1-38 (SEQ ID NO:7), 40-61 (SEQ ID NO:8), 63-82 (SEQ ID NO:9), 551-554 (SEQ ID NO:10), 556-614 (SEQ ID NO:11), 616-633 (SEQ ID NO:12), 635-653 (SEQ ID NO:13), 655-662 (SEQ ID NO:14), 664-680 (SEQ ID NO:15), 682-688 (SEQ ID NO:16), 694-697 (SEQ ID NO:17), 699-702 (SEQ ID NO:18), 704-743 (SEQ ID NO:19), 745-752 (SEQ ID NO:20), 754-758 (SEQ ID NO:21), 760-785 (SEQ ID NO:22), 789-829 (SEQ ID NO:23), 831-861 (SEQ ID NO:24), 863-887 (SEQ ID NO:25), 889-915 (SEQ ID NO:26)).

Please substitute pending paragraph [0036] with the following paragraph [0036]:

Fig. 2A-Fig. 2F depicts identified mutations (shown by arrows) at nucleotide sequence positions 1035, 1039 and 1054 of the S182 gene, PS1 locus (SEQ ID NO:3). Within the coding region, beneath each line of nucleotide sequence are the corresponding putative amino acid residues (amino acid position in Fig. 2A-Fig. 2F: 83-549 (SEQ ID NO:4), 1-38 (SEQ ID NO:7), 40-61 (SEQ ID NO:8), 63-82 (SEQ ID NO:9), 551-554 (SEQ ID NO:10), 556-614 (SEQ ID NO:11), 616-633 (SEQ ID NO:12), 635-653 (SEQ ID NO:13), 655-662 (SEQ ID NO:14), 664-680 (SEQ ID NO:15), 682-688 (SEQ ID NO:16), 694-697 (SEQ ID NO:17), 699-702 (SEQ ID NO:18), 704-743 (SEQ ID

NO:19), 745-752 (SEQ ID NO:20), 754-758 (SEQ ID NO:21), 760-785 (SEQ ID NO:22), 789-829 (SEQ ID NO:23), 831-861 (SEQ ID NO:24), 863-887 (SEQ ID NO:25), 889-915 (SEQ ID NO:26)).

Please substitute pending paragraph [0071] with the following paragraph [0071]:

Although one embodiment of the mutant PS1 gene is disclosed in Fig. 2A-Fig. 2F (SEQ ID NO:3), it should be understood that the present invention is not so limited. In particular, within the context of the present invention reference to the PS1 gene should be understood to include derivatives, analogs, or allelic variants of the gene disclosed in Fig. 1A-Fig. 1F (SEQ ID NO:1) that are substantially similar. As used herein, a nucleic acid molecule is deemed to be "substantially similar" if (a) the nucleotide sequence is derived from the coding region of the described gene and includes portions of the sequence or allelic variations of the sequences discussed above; (b) the nucleotide sequence is capable of hybridization to nucleotide sequences of the present invention under high or very high stringency (see Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY (1989)); or (c) the DNA sequences are degenerate as a result of the genetic code to the DNA sequences defined in (a) or (b).

Please substitute pending paragraph [0074] with the following paragraph [0074]:

Alternately, the PS1 gene may be isolated by PCR methods from genomic DNA, cDNA or libraries, or by probe hybridization of genomic DNA or cDNA libraries. Primers for PCR and probes for hybridization screening may be designed based on the DNA sequence of PS1 presented herein. The DNA sequence of PS1 and the corresponding predicted amino acid sequence of PS1 is presented in Fig. 1A-Fig. 1F (SEQ ID NO:2). Primers for PCR should be derived from sequences in the 5′ and 3′ untranslated region in order to isolate a full-length cDNA. The primers should not have self-complementary sequences nor have complementary sequences at their 3′ end (to prevent primer-dimer formation). Preferably, the GC content of the primers is about 50% and contain restriction sites. The primers are annealed to cDNA and sufficient cycles of PCR are performed to yield a product readily visualized by gel electrophoresis and staining. Mutations can be visualized by single strand conformation polymorphism (SSCP) analysis. The amplified fragment is purified and inserted into a vector, such as λgt10 or pBS(M13+), and propagated.